REMARKS

The present invention relates in part to methods for predicting the likelihood of a subsequent cerebral vasospasm in patients presenting with subarachnoid hemorrhage.

Claims 1, 5, 8, 11, 14-16, and 18-26 are pending herein. In the present submission, claims 2-4, 6, 7, 9, 10, 12, 13, and 17 are cancelled, claims 1, 5, 8, 11, 14, and 18 are amended, and new claims 25 and 26 are added. Support for the amended and new claims may be found in the specification for example in Example 4 beginning on page 98 and example 9, beginning on page 117, which describe the use of neural cell adhesion molecule (NCAM), vascular endothelial growth factor (VEGF), B-type natriuretic peptide (BNP), matrix metalloprotease-9 (MMP-9), caspase-3, and von Willebrand factor (vWF) in methods for characterizing the risk of future cerebral vasospasm in subjects having suffered from a subarrachnoid hemorrhage. These amendments do not add new matter.

Applicants request reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

1. 35 U.S.C. §112, First Paragraph (written description)

Applicants respectfully traverse the rejection of claims 1-24 as allegedly failing to satisfy the written description standard of 35 U.S.C. §112, first paragraph.

The rejection is premised on the assertion that "neither the specification nor the claims teach how to define or obtain 'markers related to'" the various markers recited in the claims. Office Action, page 3. This incorrect assertion is repeated throughout the rejection. *See, e.g.*, Office Action, page 4 ("The skilled artisan cannot envision the detailed structure of the 'markers related to' and 'markers related thereto'").

Applicants note that U.S. Application 10/225,082 (a parent of the present Application and assigned to the same entity as the present Application) was recently the subject of a Decision on Appeal (Appeal No. 2007-0628) with respect to a similar rejection that was likewise premised on the Written Description requirement.

In Appeal No. 2007-0628, the claims at issue referred to "related markers." As in the present specification, this term is defined in U.S. Application 10/225,082 as "one or more fragments of a particular marker that may be detected as a surrogate for the marker itself." Also likewise to the present case, the examiner in U.S. Application 10/225,082 argued that the claim encompassed a genus of fragments, and that no specifics concerning the structure or sequence of such fragments were disclosed in the specification. After considering the same arguments made by Applicants herein, The Board of Patent Appeals and Interferences reversed the rejection under the Written Description requirement in that case, stating the following (emphasis added):

> Appellants have asserted that all the proteins recited in the claims are known in the art, and the Examiner has not disputed that assertion. **Thus, the "related markers" recited in the claims are merely fragments of known proteins. We agree with Appellants that the sequences of known proteins, and fragments of them, are readily available to those skilled in the art. "[T]here is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure."** Falkner v. Inglis, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). "Indeed, [such a requirement], if one existed, would serve no goal of the written description requirement." Id. at 1368, 79 USPQ2d at 1008.
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> The Examiner has not established that the claims are unpatentable under 35 U.S.C. § 112, first paragraph. The rejection of claims 45, 47, 50, 53-69, and 73 for lack of adequate written description is reversed.

A copy of the Decision on Appeal in Appeal No. 2007-0628 is included with this submission for the benefit of the Examiner. Applicants believe the arguments in, and results of, Appeal No. 2007-062 are equally applicable to the present rejection. It cannot be disputed that neural cell adhesion molecule (NCAM), vascular endothelial growth factor (VEGF), B-type natriuretic peptide (BNP), NT-proBNP, proBNP, matrix metalloprotease-9 (MMP-9), caspase-3, and von Willebrand factor (vWF) are each known proteins. In addition, the specification provides at paragraph [0093] the following definition:

> The term "related marker" as used herein refers to one or more fragments of a particular marker or its biosynthetic parent that may be detected as a surrogate for the marker itself or as independent markers. For example, human BNP is derived

> by proteolysis of a 108 amino acid precursor molecule, referred to hereinafter as BNP1-108. Mature BNP, or "the BNP natriuretic peptide," or "BNP-32" is a 32 amino acid molecule representing amino acids 77-108 of this precursor, which may be referred to as BNP77-108. The remaining residues 1-76 are referred to hereinafter as BNP1-76.

As Applicants have noted previously, and as confirmed by the above-quoted section from the Decision on Appeal in Appeal No. 2007-0628, imposing a *per se* requirement that the "related markers" must be disclosed in the specification in order to satisfy the written description requirement is contrary to the established law. Rather than any *per se* requirement that a claim limitation directed to such a macromolecular sequence must be supported by a specific sequence, the proper standard for determining compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. *See* MPEP § 2163.02 (citing *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). Because the descriptive text needed to meet the written description requirement varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence, it is important to understand the claims in that context when performing the proper written description analysis.

In the present case, the specification makes it unambiguous that the "related markers" recited in the claims are characterized by their structural relationship to the specified parent marker, and these structures are well known in the art. Thus, given the nature and scope of the invention at issue, and the scientific and technologic knowledge already in existence, the present specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. The written description requirement demands no more.

In view of the foregoing, Applicants request that the rejection be reconsidered and withdrawn.

2. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claims 1-4 and 19-24 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Jackowski, U.S. Patent 6,235,489 in view of Charpentier *et al., Stroke* 30: 1402-08, 1999. Applicants submit that no *prima facie* case of obviousness has been established.

As an initial matter, Applicants note that this rejection is repeated twice in the Office Action; once beginning on page 7, and once beginning on page 9. Applicants respectfully request clarification as to whether different rejections were intended, or whether this duplication is in error.

The Examiner asserts that "Jackowski discloses methods for assessing stroke (brain or temporal change) via the measurement of multiple markers." Office Action, page 7. Applicants note, however, that whatever Jackowski discloses, even the Examiner acknowledges that Jackowski does not disclose the claimed invention, which is a method of characterizing a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage. *See, e.g.*, Office Action, page 8 ("Jackowski differs from the instant invention in not specifically assessing the future risk of cerebral vasospasm in the subject suffering from subarrachnoid hemorrhage"). Thus, whether or not Jackowski can "distinguish and/or differentiate between ischemic and hemorrhagic events" as the Examiner contends (Office Action, page 7), is of no relevance to the present invention. What is relevant is that Jackowski provides no information on how to characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or even that such a thing could be possible.

The Examiner seeks to combine Jackowski with Charpentier *et al.*, which discloses that subject age <50 years, good neurological grade, and hyperglycemia were associated with an increased risk of cerebral vasospasm following subarrachnoid hemorrhage. *See, e.g.*, Charpentier *et al.*, page 1402, abstract section entitled "Conclusions." Charpentier *et al.* does not, however,

even suggest that protein biomarkers, such as those used by Jackowski, could be used to characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or even that such a thing could be possible. At most, Charpentier *et al.* merely establishes that cerebral vasospasm exists in such patients, and that one might characterize the risk based on certain patient characteristics.

The Examiner's reasoning for combining these publications is based on nothing more than an assertion that it is useful to characterize a risk of future cerebral vasospasm, for example to reduce intensive care stays. Office Action, page 8, final two paragraphs. But missing from the Examiner's reasoning is any basis on which one would consider using biomarkers to do so, since nothing of record in the rejection even suggests this as a possibility. Indeed, one of skill in the art would not have any reasonable expectation that the markers used by Jackowski could be used to characterize the future risk of a cerebral vasospasm, as nothing of record in the rejection even suggests this as a possibility.

As noted in *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741, (2007), rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. In the present case, while Charpentier *et al.* may show that there is a general desire to characterize a risk of future cerebral vasospasm, there is no apparent reason to do so using the method that is disclosed Jackowski, since nothing suggests the Jackowski method would have any relationship to future cerebral vasospasm.

Moreover, the claims as presently amended provide that at least one marker be selected from the group consisting of neural cell adhesion molecule (NCAM), vascular endothelial growth factor (VEGF), B-type natriuretic peptide (BNP), NT-pro BNP, pro-BNP, matrix metalloprotease-9 (MMP-9), caspase-3, and von Willebrand factor (vWF), or markers related thereto. Nothing in Jackowski or Charpentier *et al.* suggests the use of any of these markers for any purpose whatsoever.

Because no *prima facie* case of obviousness has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

3. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claims 6-8, 15, 17, and 18 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Jackowski, U.S. Patent 6,235,489 in view of Charpentier *et al., Stroke* 30: 1402-08, 1999 and Yakovlev *et al., J. Neurosci.* 17: 7415-24, 1997. Applicants submit that no *prima facie* case of obviousness has been established.

As discussed above, the Examiner's reasoning for combining these publications is based on nothing more than an assertion that it is useful to characterize a risk of future cerebral vasospasm, for example to reduce intensive care stays. Office Action, page 8, final two paragraphs. But missing from the Examiner's reasoning is any basis on which one would consider using biomarkers to do so, since nothing of record in the rejection even suggests this as a possibility. Indeed, one of skill in the art would not have any reasonable expectation that the markers used by Jackowski could be used to characterize the future risk of a cerebral vasospasm, as nothing of record in the rejection even suggests this as a possibility.

Likewise, Yakovlev *et al.* provides no information on how to characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or even that such a thing could be possible. Instead, Yakovlev *et al.* is directed to an analysis of caspase levels in traumatic brain injury caused by a rapid injection of saline into the cranial cavity, deforming the brain. As in the Examiner's suggested combination of Jackowski with Charpentier *et al.*, while there may be a general desire to characterize a risk of future cerebral vasospasm, there is no apparent reason to do so using a marker – caspase-3 – that is not discussed in Yakovlev *et al.* in relation to either subarrachnoid hemorrhage or cerebral vasospasm.

Because no *prima facie* case of obviousness has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

4. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claim 5 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Jackowski, U.S. Patent 6,235,489 in view of Charpentier *et al., Stroke* 30: 1402-08, 1999 and Ronn *et al.*,WO00/18801. Applicants submit that no *prima facie* case of obviousness has been established.

As discussed above, the Examiner's reasoning for combining these publications is based on nothing more than an assertion that it is useful to characterize a risk of future cerebral vasospasm, for example to reduce intensive care stays. Office Action, page 8, final two paragraphs. But missing from the Examiner's reasoning is any basis on which one would consider using biomarkers to do so, since nothing of record in the rejection even suggests this as a possibility. Indeed, one of skill in the art would not have any reasonable expectation that the markers used by Jackowski could be used to characterize the future risk of a cerebral vasospasm, as nothing of record in the rejection even suggests this as a possibility.

Likewise, Ronn *et al.* provides no information on how to characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or even that such a thing could be possible. The Examiner asserts that the artisan would look to Ronn *et al.* "because the prior art has established the relationship between NCAM and stroke." Office Action, page 12. This is reflective of a fatal flaw in the Examiner's analysis – the present claims are not directed to the diagnosis of stroke, as the Examiner apparently believes. Instead, the present claims are directed to characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage. Nothing in Ronn *et al.*, or indeed in any reference cited by the Examiner, establishes any relationship between any biomarker and risk of future cerebral vasospasm. As such, there is no rational underpinning to support the legal conclusion of obviousness.

Because no *prima facie* case of obviousness has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

5. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claim 5 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Jackowski, U.S. Patent 6,235,489 in view of Charpentier *et al., Stroke* 30: 1402-08, 1999 and Greenberg, Drug News and Perspectives 11: 265-70, 1998. Applicants submit that no *prima facie* case of obviousness has been established.

As discussed above, the Examiner's reasoning for combining these publications is based on nothing more than an assertion that it is useful to characterize a risk of future cerebral vasospasm, for example to reduce intensive care stays. Office Action, page 8, final two paragraphs. But missing from the Examiner's reasoning is any basis on which one would consider using biomarkers to do so, since nothing of record in the rejection even suggests this as a possibility. Indeed, one of skill in the art would not have any reasonable expectation that the markers used by Jackowski could be used to characterize the future risk of a cerebral vasospasm, as nothing of record in the rejection even suggests this as a possibility.

The secondary Greenberg publication does not cure the flaws in the Examiner's *prima facie* case, as it too is unrelated to the claimed subject matter. Instead, Greenberg relates to the use of VEGF as a marker in cerebral ischemia. Applicants note that cerebral ischemia is a different condition than either subarrachnoid hemorrhage or cerebral vasospasm. Nothing in Greenberg, or indeed in any reference cited by the Examiner, establishes any relationship between any biomarker and risk of future cerebral vasospasm. As such, there is no rational underpinning to support the legal conclusion of obviousness.

Because no *prima facie* case of obviousness has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

6. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claim 5 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Jackowski, U.S. Patent 6,235,489 in view of Charpentier *et al.,*

Stroke 30: 1402-08, 1999 and Roger *et al., J. Am. Coll. Cardiol.* 34: 155-62, 1999. Applicants submit that no *prima facie* case of obviousness has been established.

As discussed above, the Examiner's reasoning for combining these publications is based on nothing more than an assertion that it is useful to characterize a risk of future cerebral vasospasm, for example to reduce intensive care stays. Office Action, page 8, final two paragraphs. But missing from the Examiner's reasoning is any basis on which one would consider using biomarkers to do so, since nothing of record in the rejection even suggests this as a possibility. Indeed, one of skill in the art would not have any reasonable expectation that the markers used by Jackowski could be used to characterize the future risk of a cerebral vasospasm, as nothing of record in the rejection even suggests this as a possibility.

The secondary Roger *et al.* publication relates to the use of BNP as a therapeutic in decompensated congestive heart failure. Like the other publications on which the Examiner relies, Roger *et al.* provides no information on how to characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or even that such a thing could be possible.

The Examiner suggests that the artisan would look to Roger *et al.* "since stroke and vasospasms are related to blood vessel flow... [and] one of ordinary skill in the art would have evaluated BNP in order to monitor blood vessel flow as it relates to these disorders." This opinion of the Examiner is merely a conclusory statement unsupported by any evidence or other rational underpinnings that might support a conclusion of obviousness. Applicants respectfully request that the Examiner provide some evidence that BNP may be used to "monitor blood vessel flow" and that monitoring of "blood vessel flow" has been related in any way to the future risk of a cerebral vasospasm.

Because no *prima facie* case of obviousness has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date 07/24/2007

By _____

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